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## INFLUENCE OF METABOLIC THERAPY ON LIFE QUALITY IN PATIENTS WITH ATRIAL FIBRILLATION PAROXYSMS

### Вплив метаболічної терапії на якість життя хворих з пароксизмами михопітної атритії

#### Abstract

**Purpose of the study.** The goal of the study was to investigate the effect of magnesium orotate as a part of complex therapy in sinus rhythm restoring in patients with AF paroxysm, as well as to evaluate its effectiveness and effect on LQo with long-term use.

**Materials and research methods.** We examined 56 patients (16 women and 40 men) with an average age of  $(61,5 \pm 4,3)$  years with paroxysmal atrial fibrillation. All patients were divided into two groups. Patients of the 1st group ( $n = 28$ ) underwent medical cardioversion with amiodarone and magnesium orotate. Patients of the 2nd group ( $n = 28$ ) received only amiodarone. The time of sinus rhythm restoration, parameters of electrical instability of the atrial and ventricular myocardium after sinus rhythm restoration, patients life quality 3 months after discharge – were assessed in both groups.

**Results.** The study allowed to reveal that the addition of magnesium orotate to the basic therapy of patients with atrial fibrillation increases the effectiveness of medical cardioversion and reduces the time of its onset. When using amiodarone and magnesium orotate, signs of electrical instability of the atrial myocardium (the number of paired and supraventricular extrasystoles) are significantly less according to the results of Holter electrocardiogram monitoring compared with amiodarone monotherapy. Atrial fibrillation caused a life quality parameters deviations in the form of an increase in the severity of the disease symptoms, physical activity limitation and psycho-emotional sphere disorders. 3 months after the

#### Реферат

**Мета дослідження.** Вивчити вплив препарату оротату магнію у складі комплексної терапії при відновленні синусового ритму у хворих із пароксизмом фібриляції передсердь, а також оцінити його ефективність та вплив на якість життя при тривалому використанні.

**Матеріали та методи дослідження.** Обстежено 56 пацієнтів (16 жінок та 40 чоловіків) середній вік, яких склав  $(61,5 \pm 4,3)$  рік із пароксизмом фібриляції передсердь. Усі пацієнти були розподілені на дві групи. Пацієнтам 1-ї групи ( $n = 28$ ) проводилася медикаментозна кардіоверсія аміодароном та призначався оротат магнію. Пацієнти 2-ї групи ( $n = 28$ ) отримували лише аміодарон. Оцінювали час до відновлення синусового ритму в обох групах, електричну нестабільність міокарда передсердь та шлуночків після відновлення синусового ритму, якість життя пацієнтів через 3 місяці після виписки.

**Результати.** У ході дослідження зазначено, що додавання до базової терапії пацієнтів із фібриляцією передсердь препарату оротату магнію збільшує ефективність медикаментозної кардіоверсії та скорочує час її настання. При використанні аміодарону та оротату магнію достовірно рідше виявляються при холтерівському моніторингу електрокардіограми ознаки електричної нестабільності міокарду передсердь (кількість парних та суправентрикулярних екстрасистол) порівняно з монотерапією аміодароном. Фібриляція передсердь викликала погіршення показників якості життя у вигляді посилення вираженості симптомів захворювання, обмеження фізичної активності,

*treatment, it was noted that life quality in patients of the 1st group (complex therapy using magnesium orotate) was higher compared to patients of the 2nd group due to the improvement in the indicators of the «psycho-emotional» component.*

**Conclusions.** *The addition of magnesium orotate to the basic therapy of paroxysmal atrial fibrillation can significantly improve the clinical course of the disease in patients and their life quality after 3 months treatment period.*

**Keywords:** *atrial fibrillation, medical cardioversion, amiodarone, magnesium orotate, life quality.*

*порушень у психоемоційній сфері. Через 3 місяці лікування пацієнтів зазначено, що якість життя при комплексній терапії із використанням оротату магнію у пацієнтів 1-ї групи була вищою порівняно з пацієнтами 2-ї групи за рахунок покращення показників «психоемоційного» компоненту.*

**Висновки.** *Додавання оротату магнію до складу базисної терапії пароксизму фібриляції передсердь дозволяє достовірно покращити клінічну картину у пацієнтів та показники якості життя через 3 місяці його використання.*

**Ключові слова:** *фібриляція передсердь, медикаментозна кардіоверсія, аміодарон, оротат магнію, якість життя.*

Atrial fibrillation (AF) is one of the most common cardiac arrhythmias. According to current researches, its prevalence in the developed world is approximately 1,5–2,0% of the total population [8]. The increased interest in the need to treat AF is due to the fact that it increases the risk of stroke by 5 times, congestive heart failure by 3 times, the risk of death from all causes by 2 times and from cardiac causes by 2,4 times [10]. AF, in addition to medical, is also a serious socio-economic problem. It has been established that the total cost of managing patients with AF during the year after the first hospitalization is more than the treatment of patients with sinus rhythm, not counting expensive types of emergency care.

Treatment of patients with paroxysmal and persistent AF is a key problem of modern arrhythmology, which trend is primarily at preventing cardiovascular accidents. However, to achieve this goal, it is necessary to solve a number of tactical tasks, such as symptom relief and a decrease in the frequency of episodes of AF paroxysms, which improves the life quality (LQo). The absence of undesirable changes in various subspheres of LQo is the key to successful treatment of AF, primarily due to good compliance to such treatment. According to the latest recommendations of the European Society of Cardiology, several drugs are used for this goal: amiodarone, flecainide, ibutilide, propafenone and vernakalant, but amiodarone is most common used in cardiology practice to restore heart rhythm [7].

The Euro Heart Survey on Atrial Fibrillation trial found out that coronary heart disease (CHD) is one of the most frequently associated diseases in patients with AF. Every fourth patient with AF was diagnosed with CHD, and half of the patients included in the study were diagnosed with CHD in combination with essential hypertension [9]. In the complex treatment of patients with chronic coronary artery disease, metabolic agents are used to improve the efficiency of oxygen utilization by the myocardium under conditions of ischemia [11].

Trimetazidine is currently considered as the etalon among other metabolic agents. However, despite the anti-ischemic efficacy, trimetazidine has no antiarrhythmic effect. This leads to the search for new agents, which, along with the cytoprotective (antihypoxic) effect, would help to reduce arrhythmias.

The Framingham Heart Study clearly demonstrated that prolonged hypomagnesaemia correlates with a high incidence of ventricular extrasystoles, tachycardia, and ventricular fibrillation. In the PROMISE Study it was shown that a higher incidence of ventricular premature beats and high mortality was found in the group of patients with hypomagnesemia compared with groups in which normo- and hypermagnesemia were noted. The results of the randomized, multicenter, placebo-controlled, double-blind MAGICA study made it possible to consider magnesium agents as a generally accepted European standard for the treatment of arrhythmias in patients receiving cardiac glycosides, diuretics, and antiarrhythmic drugs [2].

The goal of the study was to investigate the effect of magnesium orotate as a part of complex therapy in sinus rhythm restoring in patients with AF paroxysm, as well as to evaluate its effectiveness and effect on LQo with long-term use.

## MATERIALS AND RESEARCH METHODS

The study included 56 patients (16 women and 40 men) with paroxysmal AF lasting more than 2 days but less than 1 month. The average age of the examined patients was  $(61,5 \pm 4,3)$  years. The most common diseases that caused AF were CHD (in 56 (100%) patients) and arterial hypertension (in 31 (62%)). A history of MI was in 39 (71%) subjects. Heart failure of II-III functional class according to NYHA was diagnosed in all patients, diabetes mellitus was registered in 19 (34%) patients. All patients signed out an informed consent to participate in the study.

After a thorough analysis of the anamnesis data, the results of clinical and instrumental examination, it was decided to restore the heart rhythm in all patients. Before the rhythm was restored, the target levels of blood pressure (BP) were achieved in patients, the signs of heart failure were leveled, anticoagulant therapy with warfarin was selected with an international normalized ratio of 2 to 3. All patients were randomly divided into two groups comparable in age, duration of AF paroxysm and clinical and instrumental data. Patients of the 1st group (n = 28) underwent medical cardioversion (MC) with amiodarone and were prescribed magnesium orotate (Magnerot, Werwag Pharma GmbH and Co., Germany) 6 capsules immediately at the time of hospitalization. Patients of the 2nd group (n = 28) underwent only MC. MC was carried out according to the following scheme of saturation with amiodarone: 5 mg/kg (but not more than 450 mg once) intravenously and 600 mg per os per day for 3 days, then amiodarone per os 600 mg/day for 7 days. If MC did not occur after 10 days, then patients underwent electrical cardioversion (EC). Concomitant therapy in both groups included: angiotensin-converting enzyme inhibitors or sartans,  $\beta$ -blockers, statins. The time to restoration of heart rhythm in both groups of patients, the frequency of detection of atrial and ventricular extrasystoles against the background of sinus rhythm (SR) according to ECG Holter monitoring (HM ECG) were evaluated.

The physical and emotional components of patients' LQo were assessed 3 months after discharge. Patients of the 1st group continued to take magnesium orotate at a dose of 2 tablets per day against the background of basic therapy for 2 months, patients of the 2nd group took only basic therapy. To assess the life quality, a questionnaire by R.A. Libis et al. «Quality of life in patients with arrhythmias» was used. The methodology consists of 21 questions, for each of which it is proposed to choose one of 5 answers (no effect of arrhythmia on one or another component of QOL – 0 points, a very strong effect on this component – 4 points). QOL in % was calculated using the formula:  $100\% - (K \times KB)$ , where 100% is the «ideal» quality of life; K – a coefficient of 1,19, showing the number of percent that subtracts from the «ideal» QOL each score scored in the survey; KB – the number of points scored in the survey.

Statistical processing of the obtained data was carried out using the PSPP application package (version 1.0.1, GNUProject, 1988–2017). During the analysis, methods of parametric and nonparametric variational statistics were used. The character of the variants distribution was determined by the Kolmogorov-Smirnov test, the equality of general variances was controlled using the Fisher F-criterion. The Obtained results are presented as mean values (M)  $\pm$  standard

deviation (s). To assess the relationship between the studied quantitative parameters, the Spearman rank correlation method (r) was used.

## RESULTS AND ITS DISCUSSION

During treatment with the use of amiodarone in combination with magnesium orotate, there were no changes in the general blood test, general urinalysis, levels of total bilirubin, alanine aminotransferase, aspartate aminotransferase, creatinine and blood glucose, levels of total cholesterol and sodium in the blood serum, which indicates the safety of this drug therapy. In both groups, under the influence of therapy, patients noted an improvement in their general condition, primarily due to a decrease in the sensation of palpitations. So, in the 1st group, the average score of the subjective assessment of the heartbeat before treatment was  $(4,1 \pm 1,1)$ , after treatment with amiodarone in combination with magnesium orotate –  $(1,2 \pm 0,8)$  ( $p = 0,0015$ ), and in the 2nd group – respectively  $(3,8 \pm 1,2)$  and  $(1,9 \pm 0,6)$  ( $p = 0,0015$ ).

According to the objective monitoring of hemodynamic parameters, it was found that in the amiodarone monotherapy group, BP parameters did not change significantly –  $(136,3 \pm 5,4)/ (81,5 \pm 4,7)$  mm Hg and  $(130,7 \pm 4,2)/(78,5 \pm 5,5)$  mm Hg. In group with combined treatment, an additional decrease in systolic blood pressure was noted after 12 hours of observation –  $(140,7 \pm 6,2)/ (79,1 \pm 6,7)$  mm Hg and  $(123,4 \pm 4,7)/(74,5 \pm 6,2)$  mm Hg ( $p = 0,001$ ), which is associated with an additional antihypertensive effect of magnesium.

The results of our study indicates that the use of amiodarone was sufficiently effective to restore sinus rhythm in subjects with paroxysmal AF with moderate ventricular tachysystole and amounted to about 2/3 of the patients who participated in the study, which is comparable to the literature data. Thus, in the amiodarone monotherapy group, sinus rhythm restoration was achieved in 33 (60,4%) patients, and in the amiodarone therapy group in combination with magnesium orotate, in 38 (68,0%) patients. In 13 (24,4%) patients of the 1st group and 11 (21,3%) patients of the group 2, sinus rhythm was restored after more than 48 hours. Patients in whom HR recovery was not be achieved with MC underwent transesophageal pacing.

After the SR was restored, on the 3rd day, the patients underwent HM ECG to assess the electrical instability of the atrial and ventricular myocardium (table). It was noted that when magnesium orotate was used in complex therapy, supraventricular extrasystole and paired supraventricular extrasystole revealed significantly less frequently ( $p < 0,001$ ).

According to the literature data, magnesium is one of the most important microelements in the body and provides ionic membrane processes

in both nerve and muscle cells, and orotic acid causes a powerful impact on protein metabolism, and through it on other types of metabolism – carbohydrate, lipid and water-salt [12]. Acting as a natural calcium antagonist, magnesium takes part in muscle fiber relaxation, reduces platelet aggregation, and maintains a normal transmembrane potential in electrically excitable tissues [1]. In addition, magnesium provides suppression of nerve centers that stimulate sympathetic innervation and the renin-angiotensin system, and also enhances sodium excretion due to increased renal blood flow, ensuring the removal of excess sodium from the body as one of the important factors in increasing vascular tone. It was shown in several large studies, that the magnesium has ability to prevent and stop both supraventricular and ventricular extrasystole, as well as other supraventricular arrhythmias. Orotic acid has a powerful metabolic activity, being one of the initial metabolic precursors of pyrimidine nucleotides, i.e. necessary for the normal process of anabolic reactions in all human tissues and organs. Many researchers suggest that the hypomagnesemia degree can serve as an marker of the severity of cardiovascular diseases and partly explain the severity of their symptoms [6, 15]. According to numerous studies, magnesium orotate was effective as a maintenance agent after atrial fibrillation paroxysm elimination [13]. In this view, the administration of magnesium agents, especially in combination with a protein metabolism

stimulator – orotic acid, is appropriate and fully justified in most cardiovascular pathologies [4].

3 months after SR restoration, LQo was studied in patients of both groups. Assessment of LQo showed that initially for the majority of patients in both groups unpleasant sensations in the heart area, general weakness, increased fatigue, involuntary fixation of attention on the work of the heart, expectation of palpitations, interruptions in the work of the heart, fear of cardiac attack, anxiety for one's health and life, decreased mood, feeling of depression were characteristic. Also, they were worried about the need for constant treatment, changes in relationships with loved ones. In general, in patients of both groups with AF, the initial (before treatment) LQo was 51,35%.

The dynamics of LQo in patients with AF during treatment is shown in the figure. In the group of patients who received, in addition to standard agents, magnesium orotate, LQo was 64,88%, which is 15,66% more than the original ( $p = 0,015$ ). The QoL of patients in this group before treatment was 49, 22%. The main reasons for the decrease in QoL after treatment in this group of patients were mainly due to the «physical» component. In the 2nd group of patients, the average QoL before treatment was 49,03%. On re-examination, QoL was 54,73%. The difference with the original data is 5,70% ( $p = 0,015$ ). The main reasons for the decrease in QoL after treatment in this group of patients were due to the «physical» and «emotional» components.

Table 1

Parameters of atrial and ventricular myocardium electrical instability in the examined patients

Parameter	The value of the indicator in groups	
	The first group (n = 28)	The second group (n = 28)
Heart rate average, per min	77,2 ± 5,9	75,6 ± 7,4
Supraventricular extrasystolia	310 ± 46*	583 ± 86
Paired supraventricular extrasystole	21 ± 3*	46 ± 5
Short paroxysms of AF (up to 5 min)	3 ± 1	4 ± 1
Ventricular extrasystole	246 ± 66	248 ± 65
Paired ventricular extrasystole	18 ± 4	18 ± 4

Note: \* – parameters difference significant compared with those in patients of the 2nd group ( $p = 0,001$ )

According to the literature data, one of the important effects of magnesium is the inhibition of excitation processes in the cerebral cortex and the associated implementation of narcotic, hypnotic, sedative, analgesic and anticonvulsant effects. It has been proven that the normal level of magnesium in the body ensures the activity of one of the most important amino acids neurotransmitters – glycine, which is involved in such important neurological functions as ensuring

fine muscle motor skills, accuracy of movements, pose maintaining and walking. Even when received from without in the form of glycine preparations, against the background of magnesium deficiency, it cannot fully realize its neuroprotective effects, since glycine must be activated by magnesium. Therefore, some authors suggest that magnesium, which is a significant key neuroactive element, acts on elemental homeostasis according to the cascade principle, and its deficiency disrupts,

as one of the important links, the whole chain of adaptive reactions of the body [5]. In psychiatry and neurology, magnesium is used to correct metabolic disorders and as a sedative, including for the treatment of anxiety. It is also known that magnesium ions in the extracellular fluid inhibits the release of neurotransmitters (acetylcholine and catecholamines). Due to this, magnesium has an inhibitory effect on the central nervous system, relaxes muscle fibers, thus being a natural anti-

stress factor. Magnesium and orotic acid are the best combination for two main reasons: magnesium will provide improved sleep, good rest, reduce irritability, mood instability and similar signs of neurosis, while another compound – orotic acid will help increase concentration, improve memory, optimize storing and reproducing memory engrams, increasing mental and general performance [3].

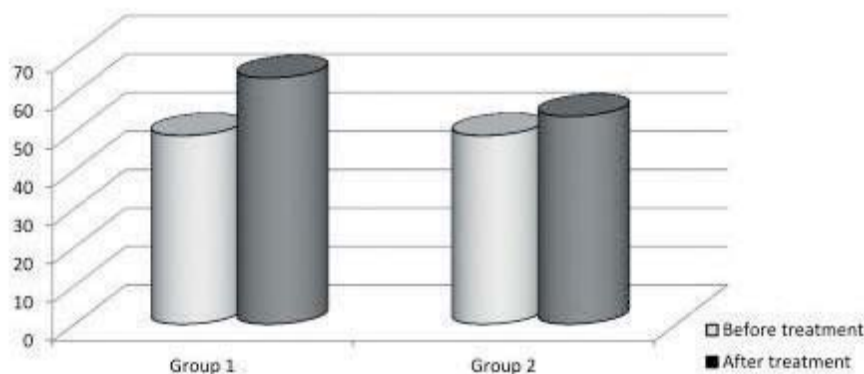


Figure 1. Changes in the life quality (in %) in patients with AF while taking magnesium orotate in comparison with patients on basic therapy

## CONCLUSIONS

1. The addition of magnesium orotate to the basic therapy in patients with atrial fibrillation increases the effectiveness of medical cardioversion and reduces the time of its onset.

2. With the combined use of amiodarone and magnesium orotate during Holter monitoring of the electrocardiogram, signs of electrical instability of the atrial myocardium (the number of supraventricular and paired extrasystole) are significantly less compared with amiodarone

monotherapy.

3. AF causes a worsening of LQo parameters in the form of an increase in the severity of symptoms of the disease, limitation of physical activity and disorders in the psycho-emotional sphere.

4. 3 months after treatment of patients with AF, it was revealed that the life quality in complex therapy with the use of magnesium orotate in patients of the 1st group is higher in comparison with patients of the 2nd group due to the improvement of the «psycho-emotional» component.

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